UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

PD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/043,665	10/05/98	RUSSELL S	MEWB112010

HM22/0106

KATHLEEN M. WILLIAMS
BANNER & WITCOFF, LTD.,
28 STATE STREET
28TH FLOOR
BOSTON, MA 02109

EXAMINER	
SHUKLA,R	
ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 01/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/043,665	Russell et al
Examiner	**Group Art Unit**
Ram Shukla	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *13-21* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of the invention of group I, claims 1-12 in Paper No 10 is acknowledged.

2. Claims 13-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10, filed 11-15-99.

3. Claims 1-21 are pending in the instant application.

4. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition of cells made by claim 1 that would have a nucleic acid encoding a polypeptide for treating a disease or disorder, does not reasonably provide enablement for a method for treatment of a patient by administering to the patient effective amount of these cells . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to making and practicing the invention commensurate in scope with these claims.

Claim 10 is directed to a pharmaceutical composition of cells that have a nucleic acid encoding a polypeptide for treating a disease or disorder incorporated into their genome. Claims 11 and 12 recite a method of treatment of a disease in a patient using said cells of claim 9 and the cells are administered by implantation into the patient.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When claims are interpreted in light of the specification, claims 10-12 are interpreted as pharmaceutical composition and methods for ex vivo gene therapy using cells that have a nucleic acid that encodes a candidate growth factor, for example stem cell factor or flt3 ligand, and such a growth factor will treat a disease or disorder that would respond to the said growth factor.

The specification in examples 1-4 (pages 14-25) discloses method of making retroviral vectors, retrovirus producer cells, packaging cells, infection of cells (progenitor cells from umbilical cord blood and hematopoietic stem cells), characterization of such cells and the proteins produced by these cells by immunoblotting and targeting of cells using said vectors. However, the specification does not provide any guidance as to the methods used for treatment of a patient using these cells. Furthermore, the specification does not provide any evidence whether the stem cells or progenitor cells or any other population of cells that would have harbored a growth factor-envelope fusion protein encoding nucleic acid would have resulted in the treatment of a disease.

In the currently presented format, claims would encompass treatment of any disease using any cells, although the specification discloses methods of infecting hematopoietic stem cells and progenitor cells. However, the art of gene therapy is highly unpredictable. Some of the relevant enablement issues are: what would be the immunological implications of the transplantation or administration of cells that would be expressing the growth factor because in the currently presented format claimed invention would encompass allogeneic, xenogeneic as well as autologous transplantation of stem cells as well as any other cells. It is well known in the art that one major problem of cell transplantation is rejection of the transplanted cells by the host (see first two paragraphs on page 54 of Kohn DB. Clin. Exp. Immunol. 107:54-57, 1997). Claims do not mention whether the cells being used for administration and transplantation are xenogeneic, allogeneic or autologous and what would have been the immunological implications of the administration of said cells or what would have been the rejection rate in the patients.

Furthermore, the method will be complicated by the effect of the growth factor or other protein to be produced in the cell and what would have been the effect of interaction of such a factor on the immunological reaction/rejection of the administered cells. Other formidable problems of hematopoietic stem cell therapy are: gene transfer of the appropriate disease related genes into a high percentage of the reconstituting hematopoietic stem cells and expression of the gene at a level which will correct the disorder without causing problems. Yet another problem is the quiescent state of stem cells that reduces their transduction with retroviral vectors because retroviral vectors infect only dividing cells.

While the method of the current invention may result in proliferation of stem cells due to induction with flt3 ligand or stem cell factor, it remains unclear whether pharmacological dosages of flt3 can induce proliferation of stem cells without causing them to enter into a terminal differentiation pathway (see last but one paragraph in column 2 on page 55 of Kohn DB, 1997). The specification does not provide any evidence or guidance whether the stem cells expressing flt3 ligand or stem cell factor would have entered the terminal differentiation pathway. Furthermore, the specification does not provide what would be the transplantation potential of the stem cells that have been multiplied ex vivo in culture because it is known in the prior art that culturing and transducing CD37+ cells for longer periods of time in presence of growth factors such as stem cell factor flt3 ligand, IL-3 and IL-6 may be detrimental for ex vivo gene transfer applications since the transduced cells are likely to have decreased potential for long term engraftation and repopulation in vivo (see abstract, Briones et al. Haematologica 84:483-488, 1999).

Yet another problem is: what would be the level of gene expression and would be sufficient to produce any treatment. The specification does not provide any example or any evidence or disclosure about the gene expression levels of the candidate therapeutic gene or growth factor when the cells are transplanted in a patient. This issue will be further compounded by the differentiation of the stem cells into their lineage specific cells and based on the stage of stem cell differentiation, the therapeutic protein may have different effects on the cell physiology. The specification does not provide any guidance regarding the efficiency of gene expression (of candidate therapeutic protein) and what would be the effect of such a protein on the physiology

of other cells in the patient. Anderson WF (1998) reviewed the current state of the art of gene therapy and he summed up his evaluations as " Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease". He also raised the issue of long-term, stable gene expression at an appropriate level and added "this is perhaps the greatest shortcoming of present vectors" (Anderson WF Nature 392:25-30, 1998).

The specification does not provide any guidance how any artisan would have dealt with the art recognized and specific issues mentioned above without undue experimentation. In conclusion while the specification is enabling for making a cell composition that has been transduced with a retroviral particle that expresses a fusion protein of a growth factor and envelope is not enabling for a method of treating a patient using said cells and therefore, limitation of the scope of the invention to a composition of cells that comprise a nucleic acid that encodes a growth factor is proper.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 1,2, 4-5, and 7- 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Ralph et al (US 5,736,387, 4-7-1998, effective filing date 6-1-94).

Claim 1 recites method of transforming a population of quiescent cells using a retroviral packaging cell line that expresses a growth factor encoding nucleic acid or retroviral particles that express a fusion of viral envelope protein with a growth factor so that the growth factor is displayed on the surface of the cell line or the viral particle and wherein the binding of the growth factor induces target cells to divide and the nucleic acid encoding the growth factor is incorporated into the genome of the cells. Dependent claims limit the quiescent cells to

hematopoietic stem cells. The invention of claim 1 is further limited to a fusion protein wherein the growth factor is attached to the N-terminal of retroviral envelope protein that is required for recognizing and binding to cellular receptors. Claim 9 recites a population of cells produced by the method of claim 1 and cells comprise a nucleic acid that encodes a polypeptide for treating a disease or disorder.

Ralph et al teach envelope fusion vectors that can be used in gene delivery. The vectors comprise chimeric targeting proteins that specifically alter the host range of the vector and the chimeric or fusion protein contains a ligand moiety that binds to receptors present on target cells and an uptake moiety that is capable of promoting the entry of the vector into the target cell. The ligand moiety is a cytokine that acts upon target cells and the uptake moiety is derived from a retroviral envelope protein (see abstract). Ralph et al teach a vectors wherein IL-2 encoding sequences are fused at the N-terminal of envelope sequences of amphotropic murine retrovirus or of ecotropic murine virus (see figures 2 and 4 and examples 1 and 6). They also teach packaging cells that are transfected with said vector and retroviral particles produced by these cells (see examples 2,3 and 6, also see claims). Ralph et al also teach that the fusion protein of their invention can be used to modulate the targeted cells in accordance with the activity of the cognate cytokine (cytokine fusion partner of the growth factor-envelope fusion protein). They further assert that fusion protein will provide a combination of activities, such as, binding to specific target cells, delivery of the vector nucleic acid into the cell and cytokine modulation of the cells targeted. Such activities will be advantageous for in vivo gene delivery where it may be otherwise problematic or impossible to induce the targeted cells to divide and thus promote stable incorporation of the transferred gene (see lines 8-32 in column 15). Ralph et al further assert that ligand moieties derived from flk2 ligand, that is specifically expressed on early hematopoietic cells or stem cells, can also be expressed as fusion protein of their invention and such a fusion protein could be used to direct infection to lymphohematopoietic progenitor cells (see lines 56-67 of column 15 continued in lines 1-7 of column 6).

Therefore, the invention of claims 1, 2, 4-5, 7, and 9 is anticipated by Ralph et al.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al in view of Lyman et al (US 5,554,512, 9-10-1996, effective filing date 5-24-93).

Claim 3 limits the growth factor in the fusion protein of claim 1 to stem cell factor or flt3 ligand.

Teachings of Ralph et al have been summarized above. Ralph et al do not teach retroviral vector or a packaging cell line that expresses a fusion protein of stem cell factor or flt3 ligand with envelope protein.

Lyman et al teach ligands for flt3 receptors that can induce the growth, proliferation and differentiation of progenitor cells and stem cells. They also teach DNA encoding flt3 ligand, host cells transfected with cDNAs encoding flt3 ligands, methods improving gene transfer to a mammal using flt3 ligand and methods of improving transplantation using flt3 ligand. They further assert that flt3 ligand can be used in treating patients with anemia, AIDS and various cancers (see abstract). Lyman et al assert that flt3 ligand of their invention can be used to increase or mobilize the number of circulating peripheral blood progenitor or stem cells, flt3 ligand can be administered to the patient or cells isolated from a patient can be treated with it ex vivo and flt3 ligand can be administered to a patient following transplantation of the isolated stem cells to facilitate engraftation thereof (see lines 49-67 in column 3). Lyman et al further assert that a cDNA encoding flt3 ligand may be transfected into cells to ultimately deliver its gene product to the targeted cell or tissue (see lines 18-24 in column 4).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the retroviral vector of Ralph et al (that encodes a fusion protein of a cytokine and

retroviral envelope protein) by cloning the flt3 ligand cDNA taught by Lyman et al, transfect the vector in cells to make packaging cells that would produce retroviral particles that can infect stem cells and affect their proliferation due to the expression of flt3 ligand with a reasonable expectation of success because all the methods have been taught by Ralph et al and Lyman et al. An artisan would have been motivated to make such vectors and retroviral particles and cell lines because Lyman et al teach that flt3 ligand can be used to stimulate the proliferation of stem cells and Ralph et al teach that their fusion protein can be used for expression of cytokines that stimulate proliferation of progenitor cells.

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al, Lyman et al as applied to claims 1-5 and 7-9 above, and further in view of Beutler et al (US 5447851, 9-5-1999, filing date 4-3-1992).

Claim 6 limits the invention of claims 1 and 5 wherein the growth factor is fused to the envelope protein via a cleavable linker.

Teachings of Ralph et al and Lyman et al have been summarized previously in para 7 and 8. None of these prior arts teaches a fusion of a growth factor and envelope proteins via a cleavable linker.

Beutler et al teach the DNA encoding a chimeric protein comprising the extracellular domain of the receptor fused to IGG and vectors and host cells comprising said DNA (see abstract). Beutler et al assert that the presence of the linker peptide at a site within the chimeric protein which may be cleaved in a manner to separate the two protein partners of the fusion protein (see lines 9-24 in column 7).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the vector of Ralph et al to include the sequences encoding a cleavable peptide polylinker between the sequences encoding the growth factor and the envelope protein with a reasonable expectation of success because Beutler et al disclose the method and sequence incorporating the linker in the fusion protein. An artisan would have been motivated to introduce

the linker in the fusion protein because that would have allowed cleavage of the growth factor from the envelope protein and this would have facilitated the action of the growth factor on the physiology of the infected cell.

12. Therefore, the claimed inventions would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Jasemine C. Chambers

JASEMINE CHAMBERS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600